The amendments to the specification at pages 2 and 28 are being made to correct minor informalities in the specification. The amendments to the specification at page 23 are being made to comply with the requirements for Sequence Listing Rules under 37 C.F. R. § 1.821-§ 1.825 which require that sequence identifier numbers be assigned to sequences disclosed in the specification (37 C.F.R. 1.821(d)). Thus, no new matter is added by these amendments. Reconsideration of the application in view of the following remarks is respectfully requested.

## REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 2, 8, 9, 15 and 20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Cancellation of claims 2, 9, 15 and 20 render the Examiner's rejections with respect to those claims moot. As per the Examiner's suggestion, Claims 1, 8 and 15 have been amended to "refer more explicitly to an antisense which is targeted to the gene encoding (i.e., human or mouse) glycosylceramide synthase of a particular sequence." Specifically, Claims 1,8, and 15 have been amended to recite that the antisense glycosylceramide synthase comprises a nucleic acid sequence. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

## REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-20 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Specifically, the Examiner contends that

the specification "does not reasonably provide enablement for a method of reversing drug resistance to all drugs and inducing apoptosis in all cancer cells comprising the introduction of any and all antisense targeting all glucosylceramide synthase genes." Cancellation of Claims 2, 9, 15 and 20 render the Examiner's rejection with respect to those claims moot. Applicants traverse the rejection with respect to the remaining claims for the reasons presented below.

The instantly claimed invention is directed to methods of for reversing drug resistance in cancer cells (e.g., Claims 1, 3-7) or methods of inducing apoptosis in a cancer cell by introducing an antisense glycosylceramide synthase (GCS) nucleic acid sequences into cancer cells (e.g., Claims 8, 10-14) and formulations comprising an antisense GCS nucleic acid sequence and a chemosensitizer or chenotherapeutic agent (e.g., Claims 15, 17-19). The instant specification teaches a variety of antisense GCS nucleic acid sequences that may be used in the disclosed methods and formulations (e.g., page 10, lines 26-28 and page 11, lines 1-28) and modifications that can be made to antisense GCS nucleic acid sequences to enhance stability and the like (e.g., page 11, lines 29-30 and page 12, lines 1-29). The specification also teaches vectors into the which the antisense GCS nucleic acid sequences may be inserted for both *in vitro* and *in vivo* use (e.g., page 14, lines 21-28 and page 15, lines 1-14). Further, the specification teaches how the antisense GCS nucleic acid sequences may introduced into a cancer cell either *in vitro* or *in vivo* (e.g., page 15, lines 15-29 and page 18, lines 23-30) and numerous cancer cells and or diseases (e.g. page 14, lines 1-20; page 15, lines 28-29 and page 16, lines 1-9) to which the instant methods and formulations may be applied. While the specific embodiment exemplified in the specification uses antisense GCS nucleic acid sequencesis *in vitro* in breast cancer cells, the specification teaches how to make and use the invention both *in vitro* and *in vivo* in a variety of cells. Applicants need not exemplify every possible claimes embodiment (e.g., all

cells, all drugs, all modes of administration). In re Robins 429 F. 2d 456,456-457, 166 U.S.P.Q. 556, 555 (CCPA 1970). Applicants therefore request withdrawal of this ground of rejection.

Moreover, Claims 15, 17,18 and 19 are directed to formulations comprising antisense GCS and a chemosensitizer or chemotherapeutic agent. The rejection is based on the premise that the instantly claimed formulations only have utility in therapeutic applications. In fact the specification provides a variety of utilities for the instantly claimed formulations. For example, the formulations may be used in cells to evaluate lipid metabolism in cancer cells (*e.g.*, page 13, lines 28-29), study diseases where regulation of apoptosis and proliferative capacity are tightly coupled. (e.g., page 4, lines 6-8, page 13, lines 24-29), drug screenings for potential cancer therapies (e.g., Examples 1-3), and in vetinary medicine (*e.g.*, page 18, lines 10-21). Applicants need only disclose one utility for the claimed invention to satisfy 35 U.S.C. § 101. In re Gottlieb 328 F.2d 1016, 140 U.S.P.Q. 665, (CCPA 1964). In re Malachowski, 530 F.2d 1402, 189 U.S.P.Q.432, (CCPA 1976).. Accordingly, Applicant respectfully request withdrawal of this ground of rejection.

To support the rejection under 35 U.S.C. § 112, first paragraph, the Examiner also cites to general reviews of gene therapy with emphasis on antisense technology. While not acquiescing to the validity of the rejection, Applicants point out that Claims 15, 17, 18 and 19, are *directed to formulations* and not therapeutic methods. Thus if the formulations are novel unobvious and useful in a single application (see above ) the formulations are patentable regardless of the predictability of gene therapy.

Based on the foregoing arguments, Applicant submits that the instant disclosure provides quite sufficient information with respect to methods of for reversing drug resistance or

of inducing apoptosis in cancer cells by introducing an antisense GCS nucleic acid sequence into cancer cells and formulations comprising an antisense GCS and a chemosensitizer or chemotherapeutic agent. Accordingly, Applicant respectfully submits that the Examiner has not met his burden of providing reasons or evidentiary support for the alleged non-enablement of the instant disclosure. In re Marzocchi, 439 F.2d 220; 169 U.S.P.Q. 367 (CFCA 1971). Applicants respectfully request withdrawal of this rejection.

**REJECTIONS UNDER 35 U.S.C. § 103**

Claims 1-5 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ichikawa et al in view of Lavie et al and further in view of Milner and James insofar as "the claims are drawn to a method of reversing drug resistance in a cancer cell *in vitro* comprising the administration of an antisense specifically targeting glycosylceramide synthase." Applicants traverse this rejection for the reasons presented below.

Ichikawa et al relates to the cloning of the cDNA sequence for human GCS. Ichikawa et al describes the DNA sequence for GCS and the expression characteristics for human GCS. However, as acknowledged by the Examiner, Ichikawa et al does not teach or suggest the use of antisense GCS nucleic acid sequences to reverse drug resistance in cancer cells. Thus, Ichikawa et al does not render the claims invention obvious

Lavie et al relates to the accumulation of glucosylceramides in multidrug(MDR) cells. Lavie et al analyzes the profile of the gucosylceramides lipids that accumulate in MDR cells and the metabolism of such lipids. Lavie et al does not teach or suggest that inhibition of GCS with antisense technology would effectively reverse MDR. Such a teaching is found only in the instant disclosure. Accordingly, Lavie et al, either alone or in combination does not render the claimed invention obvious.

Milner and James are general reviews on antisense technology. Neither Milner or James teach or suggest that an antisense GCS nucleic acid sequence would reverse drug resistance in cancer cells. Absent such a teaching, Milner and James do not remedy the deficiencies of either Ichikawa et al or Lavie et al. Thus, the cited references either alone or in combination cannot render the claimed invention obvious. Accordingly withdrawal of this ground of rejection is respectfully requested.

## OBJECTIONS TO INFORMALITIES IN THE SPECIFICATION

The disclosure has been objected to as containing minor informalities in the specification at pages 2 and 28. Applicant has amended the specification on pages 2 and 28 as per the Examiner's suggestion. Accordingly, Applicant respectfully requests withdrawal of this objection.

## NOTICE TO COMPLY WITH SEQUENCE LISTING RULES UNDER 37 C.F.R. §1.821-§1.825

The application was objected to for failure to comply with the Sequence Listing rules as set forth in 37 CFR § 1.821-1.825. In response to this objection, this amendment is accompanied by a paper copy of the Sequence Listing (Exhibit 1), a computer readable copy of the Sequence Listing (Exhibit 2), and a Statement under 37 C.F.R. § 1.821(f) (Exhibit 3). Please enter the Sequence Listing (Exhibit 1) into the specification of the above-referenced application.

## CONCLUSION

Applicants respectfully submit that the claims comply with 35 U.S.C. § 112, first and second paragraph and define an invention that is patentable over the art. Accordingly, allowance is in order, and an early notification to that effect would be appreciated. Should the

Examiner in reviewing the communication have any questions or need any additional information, he is welcome to contact the undersigned at (650) 849-4902.

A fee of $445.00 (for the extension of time) is believed due. The Assistant Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. 50-1189. Docket No.: 20239-703. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

Dated: October 26, 2000

By: _____

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